

<b>Pfizer Inc.</b>	<b>PF-04995274</b>
<b>Mechanism of Action</b>	<p>5-Hydroxytryptamine 4 receptor (5-HT<sub>4</sub>) partial agonist</p> <p><a href="http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=9">http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=9</a></p> <p><a href="http://www.ncbi.nlm.nih.gov/gene/3360">http://www.ncbi.nlm.nih.gov/gene/3360</a></p>
<b>Overview</b>	<p>PF-04995274 is a potent (<math>K_i = 0.15 - 0.46</math> nM for 5-HT<sub>4</sub> isoforms a, b, d and e), selective partial agonist of the human 5-HT<sub>4</sub> receptor.</p>
<b>Safety/Tolerability</b>	<p>PF-04995274 was found to be safe and well tolerated (similar to placebo) after administration of up to 15 mg as a single daily dose for 14 days in healthy adults, including elderly, subjects.</p> <p>Nonclinical toxicology data support clinical studies up to 1 month in duration.</p>
<b>Additional Information</b>	<p>5-HT<sub>4</sub> receptor occupancy following single oral doses ranging from 0.25 to 5 mg of PF-04995274 were assessed by PET in healthy human subjects. An <math>EC_{50}</math> of 0.104 ng/ml and 100% receptor occupancy expected to be reached with a 15 mg oral dose were determined. However, PF-04995274 failed to reverse scopolamine-induced cognitive impairment in humans.</p> <p>Preclinical CNS efficacy following oral administration was demonstrated by increased brain acetylcholine levels and power of theta oscillations in the hippocampus in rats as well as increased levels of soluble amyloid precursor protein alpha in the CSF of non-human primates.</p>
<b>Suitable for and Exclusions</b>	<p>Based on the safety profile (outlined above) and CNS receptor occupancy data, PF-04995274 is well suited for targeting the 5-HT<sub>4</sub> receptor both centrally and peripherally in clinical studies up to 1 month in duration.</p>
<b>Clinical Trials</b>	<p><a href="http://www.clinicaltrials.gov/search?term=%22PF-04995274%22">http://www.clinicaltrials.gov/search?term=%22PF-04995274%22</a></p>
<b>Publications</b>	<p><a href="http://www.sciencedirect.com/science/article/pii/S1552526011023715">http://www.sciencedirect.com/science/article/pii/S1552526011023715</a></p> <p><a href="http://www.sciencedirect.com/science/article/pii/S1552526011024149">http://www.sciencedirect.com/science/article/pii/S1552526011024149</a></p> <p><a href="http://www.sciencedirect.com/science/article/pii/S1552526011020188">http://www.sciencedirect.com/science/article/pii/S1552526011020188</a></p>